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### TANDEARIL AND BUTAZOLIDIN

The frequent, serious and occasionally fatal reactions occurring with phenylbutazone (Butazolidin - Geigy) in the treatment of rheumatoid arthritis and other inflammatory conditions stimulated a search by the Geigy company for safer analogues of the parent drug (The Medical Letter, 1: 30, 1959). Oxyphenbutazone (Tandearil - Geigy), a parahydroxy analogue and active metabolite of phenylbutazone, is the first product of the search to be offered to physicians.

On the basis of present evidence, the new drug appears to offer no significant advantage over the old in terms of either effectiveness or side effects. A review of the few published clinical reports and of the manufacturer's literature indicates that toxic and hypersensitivity reactions, side effects and contraindications — as well as indications and dosage — are almost identical. Medical Letter consultants believe that neither drug should be used by patients who can get relief of symptoms with safer drugs. On the other hand, the risk can be minimized and the drugs employed effectively if the dosage is carefully supervised and the patient watched for untoward symptoms during therapy.

**INDICATIONS** - Neither drug has as broad a range of usefulness as the manufacturer's literature indicates. Clinical trials of Tandearil in acute gouty arthritis showed results similar to those obtained with Butazolidin, and either drug may be effective in patients who do not respond to oral or intravenous colchicine or who cannot tolerate it. The drugs should also be helpful in some cases of acute bursitis, peritendinitis and painful shoulder-hand syndrome. Neither drug should be used for more than a week in these conditions, and if improvement does not occur within 48 to 72 hours, the drug should be discontinued. Toxic reactions are infrequent in the dosage range of 400 to 800 mg. on the first day and a maximum of 300 to 400 mg. on the following days. There is no convincing evidence to support the claim that the drugs are effective in acute thrombophlebitis.

Butazolidin has been used by some clinicians for long-range therapy of severe rheumatoid spondylitis; despite the hazard, they find the drug much safer than radiotherapy of the spine. As for rheumatoid arthritis, Medical Letter consultants believe that Butazolidin and Tandearil should be reserved for severe cases of the disease in which the patients are unresponsive to or cannot tolerate salicylates, chloroquine, gold salts or corticosteroids. Adequately controlled clinical trials which would permit direct comparison of different anti-inflamma-

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tory drugs are few. In one well-controlled trial (C. J. Smyth, Ann. N. Y. Acad. Sci., 86: 292, 1960), objective evaluation of the effects of Butazolidin and corticosteroids in rheumatoid arthritis was attempted. The most marked improvement in inflammatory index and functional capacity appeared to follow the use of corticosteroids; in preliminary comparisons, Tandearil appeared to be as effective an anti-inflammatory agent as Butazolidin.

**SIDE EFFECTS** - Although inadequately controlled clinical trials indicate a somewhat better gastrointestinal tolerance for Tandearil than for Butazolidin, this finding can be given little weight unless it is confirmed by well-controlled and more prolonged studies in a larger number of patients. In one study (W. Graham, Canad. M. A. J., 82: 1005, 1960), the frequency of side effects was approximately equal with both drugs; but Butazolidin had to be discontinued in 8 per cent and Tandearil in 14 per cent of the patients because of the side effects.

The most frequent reactions to Butazolidin, in addition to gastrointestinal disturbances, include fluid retention and dermatitis. Exacerbation and development of peptic ulcer have also been frequent, and together with hematologic disturbances, have been the most serious reactions to the drug. As the manufacturer warns, all of these reactions may be anticipated with Tandearil. The Tandearil package insert states that "authenticated cases of agranulocytosis associated with the drug have occurred." Both drugs are contraindicated in the presence of systemic edema, either a history or the symptoms of peptic ulcer, renal, hepatic or cardiac damage, or a history of drug allergy or of blood dyscrasias; they are also contraindicated in patients receiving other potent chemotherapeutic agents.

**CAUTIONS** - To avoid severe or even fatal reactions to these drugs in long-term therapy, the dose should not exceed 300 mg. daily, and the patient should be carefully observed for untoward symptoms. If improvement does not occur within seven days, the drug should be discontinued. Hematologic examinations should be performed weekly during the first month and then every two or three weeks, as long as dosage is maintained. As the company directions for Tandearil state, "Patients using Tandearil [or Butazolidin]... should discontinue the drug and report to the physician immediately any sign of: ... Fever, sore throat, lesions of the mouth (symptoms of agranulocytosis)..." These clinical signs can be even more important than laboratory observations in the early detection of blood dyscrasias, since the blood disorders often develop very rapidly.

#### FORTESPA<sup>N</sup> AND OTHER SUSTAINED-RELEASE VITAMIN PRODUCTS

Fortespan (SKF), S. A. Vite (Ayerst) and Tri-Span (Walker) are three of many "sustained-release" therapeutic multivitamin preparations which are claimed to have important advantages over conventional vitamin products. Slow release of the water-soluble vitamins is said to result in "optimal utilization" and minimal fecal loss.

Therapeutic vitamin formulas are, of course, useful in the treatment of deficiency states or in disorders in which requirements are increased (AMA Council on Foods and Nutrition, JAMA, 169: 41, 1959). The question posed by these

"sustained-release" preparations is whether vitamins are in fact slowly or intermittently released in the gastrointestinal tract and whether such release offers an advantage to the vitamin-deficient patient.

**RESULTS OF STUDIES** - In one study with normal subjects, using urinary excretion of the vitamins as a measure of their relative availability, five sustained-release preparations were compared with standard riboflavin tablets (A. B. Morrison, et al., N. E. J. Med., 263: 115, 1960). The preparations included both multi-coated tablets and multi-pellet capsules. The availability of the riboflavin in the sustained-release preparations ranged from 15 to 64 per cent of the amount available from the standard tablets.

None of the preparations showed evidence of slow, prolonged release of riboflavin; but slow release would probably have no significance in any event. It has not been shown that superior utilization of riboflavin can be achieved by substituting repeated small doses for a single large dose, as recommended by some clinicians. M. K. Horwitt, et al. (J. Nutrition, 41: 247, 1950) found that three 2-mg. doses of riboflavin given daily at four-hour intervals were no more effective in patients with experimental ariboflavinosis than a single dose of 6 mg. given every 24 hours. In experimental studies in rats, the utilization of the B-complex vitamins was the same whether the vitamins were given once each day or continuously in the diet (H. P. Sarett and A. B. Morrison, J. Nutrition, 70: 37, 1960).

The study by Morrison, et al., cited above, confirmed an old objection to sustained-release and delayed-release preparations. Examination of the stools of three subjects who received one of the multi-coated preparations disclosed the presence of tablets containing from 11 to 110 per cent of the amounts of the different vitamins claimed to be present in the intact tablets.

In another study, the availability of the thiamine in the same five preparations included in the above study varied from 18 to 59 per cent of the amount available from a standard preparation. None of the preparations produced sustained excretion of thiamine (A. B. Morrison and J. A. Campbell, J. Nutrition, 72: 435, 1960). In this study, it was also found that about 60 per cent of a dose of riboflavin given to a normal adult is excreted in the urine, whether it is given as a single dose or in several small doses.

Fortespan capsules provide vitamins A and D in an "immediate release" single pellet. In S.A. Vite tablets, vitamins A and D are contained in the core of the tablet, the last layer to dissolve, and in Tri-Span capsules release of these vitamins is also delayed. There is no evidence that sustained-release or delayed-release of A and D offers any advantage in either absorption or utilization as compared with immediate release from a conventional capsule or liquid preparation. Sustained-release formulations may be useful for certain drugs — the antihistamines, for example — but it has not been established that sustained-release vitamin preparations possess any advantage over standard preparations in either healthy patients or in those with deficiency diseases. It is significant that the Canadian Food and Drug Directorate, on the basis of careful study of sustained-release vitamin preparations, does not permit their sale in Canada.

## TESTS OF DICUMAROL

Eight out of nine samples of Dicumarol (Bishydroxycoumarin, USP), purchased from most of the small number of drug houses which supply this anticoagulant, conformed fully to official requirements in tests just completed for The Medical Letter. One sample (see table below) was substandard, though only by a small margin. Eight of the nine samples included in the tests consisted of 50-mg. tablets and one of 50-mg. capsules (Lilly is the only company that offers Dicumarol only in capsule form).

The U. S. Pharmacopeia requires that Dicumarol tablets contain between 93 and 107 per cent of the labeled amount of the drug. The amount actually found in the different samples ranged from 89 to 105 per cent. Standards for Dicumarol capsules are set by the National Formulary, which requires that they contain between 90 and 110 per cent of the declared weight. The amount found in the Lilly capsules was 106 per cent. Both standards include identification tests and weight-variation limitations, and the Pharmacopeia requires that the tablets disintegrate within 15 minutes under specified test conditions. In the substandard sample, four of 12 tablets took 20 minutes to disintegrate.

RESULTS OF THE TESTS - The samples were purchased from the companies by a pharmacist not identified with The Medical Letter, and they were tested by a qualified commercial laboratory. The following table gives the names of the companies from which the samples were purchased, the amount of Dicumarol found (as a percentage of 50 mg.) and the list price to the pharmacist for 1000 50-mg. tablets or capsules. All of the samples, other than Lilly's, were tablets.

<u>Company</u>	Amount of Dicumarol		<u>Company</u>	Amount of Dicumarol	
	<u>Price</u>			<u>Price</u>	
Abbott	100%	\$14.52	Lustgarten	99%	\$10.50
DuMont	105	9.90	Philadelphia Ampoule		
Jan Labs.	102	9.90	(substandard)	89	6.82
Lannett	103	10.00	Premo	95	12.00
Lilly (capsules)	106	15.48	Vitarine	95	12.40

### NOTE ON DICUMAROL

Dicumarol was the first of the oral anticoagulant drugs, and many clinicians still consider it the anticoagulant of choice (The Medical Letter, 1: 85, 1959 and 2: 58, 1960). The many different anticoagulants now available vary in rapidity of onset of effect and of dissipation of effect after therapy is stopped. Some physicians prefer a coumarin derivative, others an indandione. The physician's close familiarity with the properties of whichever drug he prescribes is probably more important than the choice of any particular drug. The indandiones, in general, appear to cause side effects more frequently than the coumarins. Dicumarol has the advantage of long use and relatively low price. Warfarin, which is probably the most widely used coumarin derivative, costs the patient about twice as much as Dicumarol for equivalent doses.